ClinicalEvidence

HIV infection

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ABSTRACT

INTRODUCTION: Infection with the human immunodeficiency virus (HIV) usually leads to 8–10 years of asymptomatic infection before immune function deteriorates and AIDS develops. Without treatment, about 50% of infected people will die of AIDS over 10 years. With treatment, prognosis depends on age, CD4 cell count, and initial viral load. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent transmission of HIV? What are the effects of different antiretroviral drug treatment regimens in HIV infection? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 17 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: combination treatments containing either CCR5 inhibitors or fusion inhibitors; early diagnosis and treatment of sexually transmitted diseases (STDs); early and delayed antiretroviral treatment using triple antiretroviral regimens; non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens; nucleoside reverse transcriptase inhibitor (NRTI)- and protease inhibitor-based triple regimens (standard and boosted); postexposure prophylaxis in healthcare workers; and presumptive mass treatment of sexually transmitted diseases (STDs).

QUESTIONS

INTERVENTIONS

PREVENTIVE INTERVENTIONS

Likely to be beneficial

Unknown effectiveness

ANTIRETROVIRAL DRUG TREATMENT

Beneficial

Likely to be beneficial

Unknown effectiveness

Covered elsewhere in Clinical Evidence

HIV: mother-to-child transmission

HIV: prevention of opportunistic infections

HIV: treating tuberculosis

To be covered in future updates

Circumcision for prevention

Footnote

*No RCTs: based on consensus and known effectiveness of antiretroviral drugs in the treatment setting

Key points

- Infection with HIV usually leads to 8–10 years of asymptomatic infection before immune function deteriorates and AIDS develops.

Without treatment, about 50% of infected people will die of AIDS over 10 years. With treatment, prognosis depends on age, CD4 cell count, and initial viral load.

- Concurrent STDs increase the risk of transmission of HIV infection. Treating STDs may reduce the risk of an individual acquiring HIV, but we don't know whether it is effective on a population level.
- Antiretroviral treatment (especially combinations including zidovudine) may reduce the risk of HIV infection among healthcare workers who have been exposed to the infection.
- Triple antiretroviral treatments are now standard for people with HIV infection.

  Boosted protease inhibitor-based regimens may be more effective than standard protease-based triple regimens at reducing viral load and preventing HIV progression and death.

  Non-nucleoside reverse transcriptase inhibitor (NNRTI; efavirenz or nevirapine)-based triple regimens seem to increase viral suppression compared with standard protease inhibitor-based triple regimens, although HIV progression rates may not be reduced.

  Standard protease inhibitor-based triple regimens may be less effective than NNRTI-based triple regimens at reducing viral load.

  Nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens offer similar viral suppression to standard protease inhibitor-based triple regimens. Some NRTIs (stavudine) may be associated with lipodystrophy.
- We don't know whether combination treatments containing either chemokine (C-C motif) receptor 5 inhibitors or fusion inhibitors (enfuvirtide) or early initiation of antiretroviral treatment using triple regimens improve long-term survival.

  The decision about when to start treatment currently depends on severity of symptoms and on CD4 lymphocyte count, so that likely benefits can be balanced against risks of adverse effects of treatment.

Clinical context

DEFINITION

HIV infection refers to infection with HIV type 1 or type 2. Clinically, this is characterised by a variable period (usually about 8–10 years) of asymptomatic infection, followed by repeated episodes of illness of varying and increasing severity as immune function deteriorates, resulting in AIDS. The type of illness varies by country, availability of specific treatments for HIV, and prophylaxis for opportunistic infections. Current treatments interrupt the life cycle of the virus without effecting a cure; mutations in the viral genome result in gradual resistance drift and increasing ineffectiveness of drug treatments.

INCIDENCE/ PREVALENCE

Worldwide estimates suggest that, by November 2007, about 33.2 million people were living with HIV. [1] In 2007, there were estimated to be 2.5 million new cases of HIV and 2.1 million deaths from AIDS. [1] About 95% of HIV infections occur in resource-poor countries. [1] By 1999, occupationally acquired HIV infection in healthcare workers had been documented in at least 102 definite and 217 possible cases, although this is likely to be an underestimate. [2]

AETIOLOGY/ RISK FACTORS

The major risk factor for transmission of HIV is unprotected heterosexual or homosexual intercourse. Other risk factors include needlestick injury, sharing drug-injecting equipment, and blood transfusion. A woman infected with HIV may also transmit the virus to her baby transplacentally, during birth, or through breast milk. This has been reported in 15%–30% of pregnant women with HIV infection. Mother-to-child transmission of HIV is dealt with in a separate review (HIV: mother-to-child transmission). Not everyone exposed to HIV will become infected, although risk increases if exposure is repeated, is at high dose, or occurs through blood. There is at least a two- to fivefold greater risk of HIV infection among people with STDs. [3]

PROGNOSIS

Without treatment, about 50% of people infected with HIV will become ill and die from AIDS over about 10 years. A meta-analysis of 13 cohort studies from Europe and the USA looked at 12,574 treatment-naive people starting highly active antiretroviral therapy (HAART) with a combination of at least three drugs. [4] A lower baseline CD4 cell count and higher baseline HIV-1 viral load were associated with an increased probability of progression to AIDS or death. Other independent predictors of poorer outcome were advanced age, infection through injection drug use, and a previous diagnosis of AIDS. The CD4 cell count at initiation was the dominant prognostic factor in people starting HAART. People with the most favourable prognostic factors (aged <50 years old, not infected through injection drug use, viral load <100,000 copies/mL, and CD4 cell count >350 cells/mL on initiation of HAART) were estimated to have a 3.5% chance of progression to AIDS or death within 3 years. People with the least favourable prognostic factors (aged at least 50 years old, infected through intravenous drug use, viral load at least 100,000 copies/mL, and CD4 cell count <50 cells/mL on initiation of HAART) had an estimated 50% chance of progression to AIDS or death within 3 years. Genetic factors have been shown to affect response to antiretroviral treatment, but were not considered in the meta-analysis. [4] We found one non-systematic review assessing

prognosis in people in Africa. [5] It identified one study conducted in rural Uganda, which found similar survival rates (a median 9.8 years from the time of HIV-1 seroconversion) but found that progression to symptomatic disease was faster in Uganda than in resource-rich countries, owing largely to the high background level of morbidity. [5] The review reported that most people in hospital in Africa with HIV have the clinical features of AIDS just before they die, and many are severely immunosuppressed. The review also suggested that morbidity was similar to that in resource-rich countries before the introduction of HAART.

AIMS OF INTERVENTION To reduce transmission of HIV; to prevent or delay the onset of AIDS, as manifested by opportunistic infections and cancers; to increase survival; to minimise loss of quality of life caused by inconvenience, with minimal adverse effects.

OUTCOMES *Preventative interventions:* incidence of new HIV infections, adverse effects. *Treatment:* mortality, progression to AIDS (as defined by the revised Centers for Disease Control and Prevention criteria 1993), [6] markers of disease progression (viral load and peripheral blood CD4 lymphocyte count), quality of life, adverse effects including lactic acidosis and lipodystrophy. Most systematic review and RCTs we found analysed the outcomes of mortality and disease together; therefore, we have assessed progression to AIDs or mortality as a composite outcome throughout this review.

METHODS *Clinical Evidence* search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies.Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 individuals of whom more than 80% were followed up with a minimum of 12 weeks of follow-up. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We also searched for cohort studies on specific harms of interventions and for cohort and case control studies of postexposure prophylaxis. We excluded RCTs in children or solely in people with AIDS. Trials were included if they examined clinical end points. Where trials using clinical end points were unavailable, we included trials using surrogate markers known to denote higher risk of disease progression. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 29). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to prevent transmission of HIV?

OPTION EARLY DIAGNOSIS AND TREATMENT OF STDS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Concurrent STDs increase the risk of transmission of HIV infection. Treating STDs may reduce the risk of an individual acquiring HIV, but we don't know whether it is more effective on a population level.
- Interventions to decrease HIV transmission by reducing STDs may be effective only in regions where the HIV epidemic is emerging and infection is concentrated within a population where the incidence of STDs is high.

Benefits and harms

Early diagnosis and treatment of STDs versus control:

We found one systematic review (search date 2003, 2 RCTs) [7] and one additional RCT. [8] The two RCTs identified by the review randomised communities, which included people both with and without HIV. [7] The first RCT [9] identified by the review [7] randomised 12 pair-matched communities in Tanzania; the second RCT [10] identified by the

review [7] randomised 18 matched rural communities in Uganda. The additional RCT included female sex workers in Côte d'Ivoire who were HIV-1 seronegative. [8]

Incidence of HIV infection

Early diagnosis and treatment of STDs compared with routine care We don't know whether early diagnosis and management of STDs is more effective at reducing the incidence of HIV infections (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of HIV infection					
[9] RCT	Communities included people both with and without HIV in Tanzania In review [7] Cluster randomised — 12 pair-matched communities About 1000 people from each community were randomly selected for evaluation	**Risk of acquiring HIV , 2 years** 48/4149 (1.2%) with active intervention 82/4400 (1.9%) with with no intervention (routine care) The active intervention consisted of diagnosis and treatment of STDs at a local health centre (within 90 minutes' walking distance), provision of free condoms during the current STD episode, and health education by healthcare workers trained in STD case management Analysis included 8549 people who were HIV negative at baseline and attended 2 years' follow-up	RR 0.58 95% CI 0.42 to 0.79 (adjusted)	●○○	active intervention
[10] RCT	Communities included people both with and without HIV in Uganda In review [7] Cluster randomised — 18 matched rural communities About 96,000 people in communities	**Incidence of HIV-1 infection (incidence per 100 person years at risk)** 0.81 with improved STD management and behavioural intervention 0.80 with routine care Comparison was a community behavioural intervention, behavioural intervention plus improved STD management, or routine care at the local government health facility. The behavioural intervention provided information, education, and communication activities; the improved STD management involved training and supervising local healthcare workers and providing drugs for treatment of STDs About 20,500 people living in villages close to the community health centre were selected for evaluation; analysis included 14,658 people who provided data at baseline and follow-up	RR 1.00 95% CI 0.60 to 1.98 (adjusted)	⟷	Not significant
[8] RCT	542 female sex workers in Côte d'Ivoire who were HIV-1 seronegative	**Rate of acquiring HIV-1** 5.3/100 person-years with intensive screening 7.6/100 person-years with basic screening RCT compared a basic STD diagnosis strategy, where women were examined only if they reported symptoms of STD, versus an intensive screening strategy, where women were examined	RR 0.70 95% CI 0.25 to 1.90 P = 0.5 Analysis only included the 225 women (43%; 108 in the intensive-screening group and 117 in the basic-screening group) for whom at least one 6-monthly outcome assessment was available. The RCT included some women who were HIV-2 positive	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		every month regardless of symptoms	at baseline. It found no cases of seroconversion for HIV-2		

Adverse effects

No data from the following reference on this outcome. [8] [9] [10]

Further information on studies

Comment: **Clinical guide:**
The different effects on HIV incidence seen in the trials may, in part, reflect the epidemiological properties of mature and emerging epidemics. [7] The region of Tanzania studied in the first RCT [9] had an emerging HIV epidemic, whereas the epidemic in the region of Uganda studied in the second RCT [10] was relatively mature. In communities where the HIV epidemic is emerging, infection will tend to be restricted to the high-risk population, where STDs will have a significant role in the spread of HIV infection. In a mature HIV epidemic, infection will have spread to the general population, where STDs are less common and therefore have less of a role in HIV transmission. Thus, interventions targeting STDs may have more of an effect in communities with an emerging HIV epidemic. In addition, the background level of health-seeking behaviour in the community will clearly have an impact on the additional benefit that can be derived from early treatment and mass presumptive treatment of STDs (see comment on presumptive mass treatment of STDs, p 7).

OPTION POSTEXPOSURE PROPHYLAXIS IN HEALTHCARE WORKERS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Antiretroviral treatment (especially combinations including zidovudine) may reduce the risk of HIV infection among healthcare workers who have been exposed to the infection.
- We found no direct information from RCTs about using combinations of antiretrovirals for postexposure prophylaxis. In people with established HIV infection, combinations of antiretroviral drugs are more effective than antiretroviral monotherapy for treating HIV, suggesting that the same may be true in a prophylactic setting. However, adverse effects of antiretroviral treatments are common, especially with combination treatment, and cause a significant proportion of people receiving postexposure prophylaxis to discontinue treatment after a short time.

Benefits and harms

Zidovudine alone versus control:

We found one systematic review (search date from 1985 to 2005). [11] The review identified no RCTs on the effects of postexposure prophylaxis in healthcare workers. It identified one case control study. [12]

Incidence of HIV infection

Zidovudine alone compared with control Postexposure prophylaxis with zidovudine may be more effective at reducing the risk of HIV infection at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of HIV infection					
[12] Case control	33 healthcare workers who acquired HIV infection after occupational exposure, and 679 controls who did not acquire HIV infection despite occupational exposure In review [11] Retrospective case control study	**HIV infection , at least 6 months after exposure** with cases with controls	OR 0.19 95% CI 0.06 to 0.52 People who had acquired HIV infection were significantly less likely to have taken postexposure prophylaxis (zidovudine; a nucleoside reverse transcriptase inhibitor) compared with those who had not acquired HIV OR adjusted for confounding factors See further information on studies	●●●	postexposure prophylaxis

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Case control Included in systematic review [11]	33 healthcare workers who acquired HIV infection after occupational exposure, and 679 controls who did not acquire HIV infection despite occupational exposure Retrospective case control study	**Adverse effects** with postexposure prophylaxis with no prophylaxis The case control study found short-term toxicity (including fatigue, nausea, vomiting) and gastrointestinal discomfort occurred in 50%–70% of people with zidovudine, and caused 30% to discontinue prophylaxis	No statistical analysis reported		
[11] Systematic review SR of observational studies	1717 people 3 observational studies in this analysis	**Adverse effects** with postexposure prophylaxis with no prophylaxis The review found no RCTs but identified three observational studies. For full details see further information on studies			

Zidovudine plus other antiretroviral drugs versus control:

We found no review or RCTs of postexposure prophylaxis using combinations of antiretroviral drugs. One systematic review found three observational studies assessing the adverse effects of combinations of antiretroviral drugs (see further information on studies). [11]

Further information on studies

[11] [2] **Risk of HIV transmission** The review found that HIV transmission significantly increased with deep injury, visible blood on the device, procedures involving a needle inserted in the person's blood vessel, and if the patient had a terminal illness (deep injury: OR 15, 95% CI 6.0 to 41; visible blood on the device; OR 6.2, 95% CI 2.2 to 21; needle inserted in the patient's blood vessel: OR 4.3, 95% CI 1.7 to 12; patient with terminal illness: OR 5.6, 95% CI 2.0 to 16). [11] Case control studies are considered sufficient, because experimental studies are

hard to justify ethically, and are logistically difficult because of the low rate of seroconversion in exposed people. A review of longitudinal studies estimated that the risk of HIV transmission was 0.32% after percutaneous exposure, and 0.03% after mucocutaneous exposure (percutaneous exposure: 25 studies, 22 seroconversions in 6955 exposed people; mucocutaneous exposure: 21 studies, 1 seroconversion in 2910 exposed people). [2] [13] [11]

Adverse effects Treatment studies suggest that the frequency of adverse effects is higher in people taking a combination of antiretroviral drugs (reported in 50%–90%), which may reduce adherence to postexposure prophylaxis (24%–36% discontinued). The risk of drug interactions is also increased. Severe adverse effects, including hepatitis and pancytopenia, have been reported in people taking combination postexposure prophylaxis, but the incidence is thought to be low. One survey found that 308/492 (63%) healthcare workers were prescribed triple regimens as postexposure prophylaxis. [13] Adverse effects were common, but rarely severe or serious. Six people had severe adverse effects, but these were described as transient. [13] The review found three observational studies (1717 people) assessing the adverse effects of postexposure prophylaxis. [11] It found a significantly higher incidence of adverse effects with three-drug regimens compared with two-drug regimens (753/1179 [64%] with three drugs *v* 285/538 [53%] with two drugs; RR 1.25, 95% CI 1.14 to 1.36). [11] Combination regimens were not specified for all studies. One of the three-drug regimens comprised two nucleoside reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI), whereas the other comprised zidovudine plus lamivudine plus indinavir. One of the two-drug regimens comprised two NRTIs, and the other comprised zidovudine and lamivudine. The review found no significant differences in adverse effects between taking one drug (zidovudine) and regimens of either two drugs (various combinations) or two NRTIs plus a PI (1 observational study: 2 drugs *v* 1 drug: 67/115 [58%] with 2 drugs *v* 409/647 [63%] with 1 drug; RR 0.92, 95% CI 0.78 to 1.09: 3 drugs *v* 1 drug: 127/191 [66%] with 3 drugs *v* 409/647 [63%] with 1 drug; RR 1.05, 95% CI 0.94 to 1.18).

Comment: **Clinical guide:**
In the treatment of established HIV infection, RCTs have found that combinations of two, three, or more antiretroviral drugs are more effective than single-drug regimens in suppressing viral replication — suggesting that the same may be true in a prophylactic setting. There is also a risk that zidovudine alone may not prevent transmission of zidovudine-resistant strains of HIV. This constitutes the rationale for combining antiretroviral drugs for postexposure prophylaxis.

OPTION PRESUMPTIVE MASS TREATMENT OF STDS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Concurrent STDs increase the risk of transmission of HIV infection. Treating STDs may reduce the risk of an individual acquiring HIV, but we don't know whether it is more effective on a population level.

Benefits and harms

Presumptive mass treatment of STDs versus control:

We found one systematic review (search date 2003), [7] which identified one RCT, [14] and we found one subsequent RCT. [15]

Incidence of HIV infection

Presumptive mass treatment of STDs compared with placebo/control Early treatment using empirical antibiotics as part of a package of HIV preventive services, or presumptive mass antibiotic treatment of STDs, may be no more effective at reducing the incidence of HIV infection at 20–24 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of HIV infection					
[14] RCT Included in systematic review [7]	12,726 HIV-negative people in Uganda Design: cluster randomised — 10 community clusters Because entire community clusters were randomised in the RCT includ-	**Incidence of HIV (unadjusted incidence of HIV-1) , over 20 months' follow-up** 1.5/100 person years with mass antibiotic treatment of presumptive STD 1.5/100 person years with control Every 10 months, the intervention group received directly observed	RR 0.97 95% CI 0.81 to 1.16 (adjusted)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ed in the review, people both with and without HIV were included	treatment with antibiotics (azithromycin plus ciprofloxacin plus metronidazole), whereas the control group received a low-dose multivitamin plus iron–folate plus an antihelminthic (mebendazole)			
[15] RCT	466 female HIV-negative sex workers in Kenya Before entry to the RCT, 890 sex workers were screened, and only those seronegative for HIV were entered into the trial	**HIV-1 infection , at about 2 years' follow-up** with oral azithromycin 1 g a month with placebo Treatments were directly observed In addition, all of the women received HIV-prevention services, free male condoms, and prompt treatment of any STD	RR 1.2 95% CI 0.6 to 2.5 Results based on 341/466 (73%) women followed up	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	466 female HIV-negative sex workers in Kenya Before entry to the RCT, 890 sex workers were screened, and only those seronegative for HIV were entered into the trial	**Withdrawal because of severe epigastric pain** 3 women with oral azithromycin 2 women with placebo	Significance not assessed		
[15] RCT	466 female HIV-negative sex workers in Kenya Before entry to the RCT, 890 sex workers were screened, and only those seronegative for HIV were entered into the trial	**Adverse effects including epigastric pain, vomiting, nausea, and diarrhoea** 22 women with oral azithromycin 18 women with placebo	Significance not assessed		

No data from the following reference on this outcome. [14]

Further information on studies

Comment: **Adverse effects:**
Mass treatment means that many people without STDs will be treated unnecessarily, exposing them to risks of adverse drug reactions and possibly of drug resistance.

Clinical guide:
The varying effect on HIV incidence seen with trials of early treatment and mass presumptive treatment of STDs has several possible explanations other than variable effectiveness of the interventions. Contributing factors may include: a high incidence of symptomatic STDs between rounds of mass treatment; a low population risk for treatable STDs; intense exposure to HIV; the status of the epidemic (mature or emerging); and the level of health-seeking behaviour. [7] [14] See comment on early detection and treatment of STDs, p 3 .

QUESTION What are the effects of different antiretroviral drug treatment regimens in HIV infection?

OPTION BOOSTED PROTEASE INHIBITOR-BASED TRIPLE REGIMENS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Triple antiretroviral treatments are now standard for people with HIV infection.
- Boosted protease inhibitor (PI)-based regimens may be more effective than standard PI-based triple regimens at reducing viral load and preventing HIV progression and death.
- We found no clinically important results about boosted PI-based regimens compared with nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens. PI-based regimens have been associated with increased total cholesterol, triglycerides, and low-density lipoprotein, and some NRTIs (notably stavudine) may be associated with the development of lipodystrophy.

Benefits and harms

Boosted protease inhibitor (PI)-based triple regimens versus standard PI-based triple regimens:

We found three RCTs. [16] [17] [18]

Progression to AIDS or mortality

Boosted protease inhibitor (PI)-based triple regimens compared with standard PI-based triple regimens Boosted PI-based regimens are no more effective at 72 weeks at reducing progression to an AIDS-defining event or death (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Progression to AIDS or mortality					
[18] RCT **3-armed trial**	318 protease inhibitor-naive people	**AIDS-defining event or death , 72 weeks** 10/104 (10%) with two nucleoside reverse transcriptase inhibitors (NRTIs) plus ritonavir plus saquinavir (boosted protease inhibitor [PI]-based regimen) 10/107 (9%) with two NRTIs plus indinavir (standard PI-based triple regimen) 18/107 (17%) with two NRTIs plus ritonavir (standard PI-based triple regimen) The NRTI backbones used varied, and the number of people receiving each was unclear	P = 0.16 (between-group)	⟷	Not significant

Markers of disease progression

Boosted protease inhibitor (PI)-based triple regimens compared with standard PI-based triple regimens Boosted PI-based regimens may be more effective at reducing viral load at 24–48 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Markers of disease progression					
[16] RCT	47 protease inhibitor-naive people	**Viral load (mean plasma HIV RNA) , 24 weeks** 120 copies/mL with saquinavir plus ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) (boosted protease inhibitor [PI]-based regimen) 646 copies/mL with ritonavir plus two NRTIs (standard PI-based triple regimen)	P = 0.04	○○○	boosted PI-based regimen
[16] RCT	47 PI-naive people	**CD4 cell count , 24 weeks** 364 cells/mm^3 with saquinavir plus ritonavir plus two NRTIs (boosted PI-based regimen) 330 cells/mm^3 with with ritonavir plus two NRTIs (standard PI-based triple regimen)	P = 0.49	⟷	Not significant
[17] RCT	653 people	**Viral load (AR for HIV RNA <400 copies/mL) , 48 weeks** 245/326 (75%) with two NRTIs (stavudine plus lamivudine) plus boosted PI (ritonavir plus lopinavir) 206/327 (63%) with two NRTIs plus nelfinavir (standard PI-based triple regimen)	P <0.001	○○○	boosted PI-based regimen
[17] RCT	653 people	**Viral load (AR for HIV RNA <50 copies/mL) , 48 weeks** 67% with two NRTIs (stavudine plus lamivudine) plus boosted PI (ritonavir plus lopinavir) 52% with two NRTIs plus nelfinavir (standard PI-based triple regimen)	P <0.001	○○○	boosted PI-based regimen
[17] RCT	653 people	**Viral suppression: <400 copies/mL (estimated AR for loss of viral suppression) , 48 weeks** 34% with two NRTIs plus nelfinavir (standard PI-based triple regimen) 16% with two NRTIs (stavudine plus lamivudine) plus boosted PI (ritonavir plus lopinavir)	HR 2.0 95% CI 1.5 to 2.7 P <0.001	●○○	boosted PI-based regimen
[18] RCT **3-armed trial**	318 PI-naive people	**Proportion of people with undetectable viral load (<20 copies/mL) , 72 weeks** 58% with two NRTIs plus ritonavir plus saquinavir (boosted PI-based regimen) 51% with two NRTIs plus indinavir (standard PI-based triple regimen) 41% with two NRTIs plus ritonavir (standard PI-based triple regimen) Absolute results reported graphically	P = 0.08 (between-group)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The NRTI backbones used varied, and the number of people receiving each was unclear			

Quality of life

No data from the following reference on this outcome. [16] [17] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT	47 protease inhibitor-naive people	**Diarrhoea** 15/25 (60%) with standard protease inhibitor (PI)-based triple regimen 16/22 (73%) with boosted PI-based regime	P = 0.36 See further information on studies	⟷	Not significant
[16] RCT	47 PI-naive people	**Circumoral paraesthesia** 13/25 (52%) with standard PI-based triple regimen 10/22 (46%) with boosted PI-based regimen	P = 0.65	⟷	Not significant
[16] RCT	47 PI-naive people	**Asthenia** 10/25 (40%) with standard PI-based triple regimen 4/22 (18%) with boosted PI-based regimen	P = 0.10	⟷	Not significant
[16] RCT	47 PI-naive people	**Nausea** 7/25 (28%) with standard PI-based triple regimen 7/22 (32%) with boosted PI-based regimen	P = 0.78	⟷	Not significant
[16] RCT	47 PI-naive people	**Dysgeusia** 7/25 (28%) with standard PI-based triple regimen 6/22 (27%) with boosted PI-based regimen	P = 0.96	⟷	Not significant
[17] RCT	653 people	**Diarrhoea** 56/327 (17%) with standard PI-based triple regimen 51/326 (16%) with boosted PI-based regimen	Reported as not significant See further information on studies	⟷	Not significant
[17] RCT	653 people	**Nausea** 15/327 (5%) with standard PI-based triple regimen 22/326 (7%) with boosted PI-based regimen	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] RCT	653 people	**Abdominal pain** 10/327 (3%) with standard PI-based triple regimen 13/326 (4%) with boosted PI-based regimen	Reported as not significant	⟷	Not significant
[17] RCT	653 people	**Asthenia** 11/327 (3%) with standard PI-based triple regimen 13/326 (4%) with boosted PI-based regimen	Reported as not significant	⟷	Not significant
[17] RCT	653 people	**Headache** 6/327 (2%) with standard PI-based triple regimen 8/326 (3%) with boosted PI-based regimen	Reported as not significant	⟷	Not significant
[17] RCT	653 people	**Dyspepsia** 7/327 (2%) with boosted PI-based regimen 1/327 (1%) with standard PI-based triple regimen	P <0.05	○○○	standard PI-based triple regimen
[17] RCT	653 people	**Serum triglyceride levels (>750 mg/dL)** 29/312 (9%) with boosted PI-based regimen 4/318 (1%) with standard PI-based triple regimen	P <0.001	○○○	standard PI-based triple regimen
[18] RCT **3-armed trial**	318 PI-naive people	**Discontinued assigned PI treatment** 22/104 (21%) with boosted PI-based regimen 57/107 (53%) with ritonavir-based regimen 13/107 (12%) with indinavir-based regimen	P <0.01 (between-group analysis) See further information on studies		

Boosted protease inhibitor (PI)-based regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz or nevirapine)-based triple regimens:

We found one systematic review (search date 1997–2005, 12 RCTs, 3337 people, range of duration of trials of 32–192 weeks) comparing PI-based triple regimens versus NNRTI-based triple regimens. [19] Ten of the RCTs identified by the review were open label and five were published only as abstracts. The review classified ritonavir given in boosting doses with another PI as one PI, but carried out a subgroup analysis of ritonavir-boosted PI-based triple regimens versus NNRTI-based triple regimens for the outcome of virological suppression.

Progression to AIDS or mortality

No data from the following reference on this outcome. [19]

Markers of disease progression

Boosted protease inhibitor (PI)-based triple regimens compared with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens Ritonavir-boosted PI-based triple regimens may be less effective than efavirenz- or nevirapine-based triple regimens at virological suppression (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Markers of disease progression					
[19] Systematic review	410 people 3 RCTs in meta-analysis	**Virological suppression** with NNRTI-based triple regimens with ritonavir-boosted PI-based triple regimens Absolute results not reported	OR for NNRTI *v* PI 2.00 95% CI 1.34 to 3.00	●○○	NNRTI-based triple regimens

Quality of life

No data from the following reference on this outcome. [19]

Adverse effects

No data from the following reference on this outcome. [19]

Boosted protease inhibitor (PI)-based regimens versus triple nucleoside reverse transcriptase inhibitor (NRTI) regimens:

We found no systematic review or RCTs.

Further information on studies

[16] [17] [18]

Adverse effects — boosted protease inhibitor (PI)-based triple regimens versus standard PI-based triple regimens One RCT found no significant difference in adverse effects between the boosted PI-based regimen and the standard PI-based triple regimen (overall figures not reported). [16] In another RCT, lipodystrophy or lipoatrophy were reported in 6% of people receiving the standard PI-based triple regimen and in 5% of people receiving the boosted PI-based regimen (significance not reported). [17] One person in the boosted-PI group died of pancreatitis and also had lactic acidosis. [17] A further RCT reported that renal adverse effects were more common in the indinavir group, and gastrointestinal or nervous-system adverse effects were more common with the ritonavir-based standard PI triple regimen (no further data reported). [18]

Comment:

Lipodystrophy syndrome:
See option on standard protease inhibitor-based triple regimens, p 16 .

Hyperlactataemia and lactic acidosis:
See option on standard protease inhibitor-based triple regimens, p 16 .

Resistance with boosted protease inhibitor (PI)-based regimens versus standard PI-based triple regimens:
The second RCT found no PI resistance among a sample of 37 people receiving boosted PI who had developed virological failure, whereas 25/76 (33%) people receiving the standard PI-based triple regimen who had developed virological failure showed PI resistance. [17] Resistance to

lamivudine was less common in the boosted-PI group than in the standard-PI group. [17] Pharmacokinetic data are striking enough to persuade many clinicians of the potential therapeutic advantage of this approach, and it has become common practice. [20] [21] The extent to which boosting increases the plasma levels of PIs depends on the PI used. However, similar levels of viral suppression should be achievable with any boosted PI with dose titration of ritonavir. [18] The long-term risks of combined PI treatment are unknown. [21]

Clinical guide:
Standard of care in most countries is to boost PI therapy with a small dose of ritonavir. This leads to improved and more sustained PI drug levels and may be associated with reduced rates of antiretroviral resistance. Additionally, dietary restrictions on the use of some PIs are eased and, paradoxically, pill burden may be reduced, resulting in enhanced adherence to therapy.

Drug safety alert:
A drug safety alert has been issued on the risk of changes to the electrical activity of the heart (prolonged PR or QT intervals) associated with the use of saquinavir in combination with ritonavir (www.fda.gov).

OPTION NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) (EFAVIRENZ OR NEVIRAPINE)-BASED TRIPLE REGIMENS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Triple antiretroviral treatments are now standard for people with HIV infection.
- Non-nucleoside reverse transcriptase inhibitor (NNRTI: efavirenz or nevirapine)-based triple regimens seem to increase viral suppression compared with standard protease inhibitor (PI)-based triple regimens, although HIV progression rates may not be reduced.
- Standard PI-based regimens have been associated with increased total cholesterol, triglycerides, and low-density lipoprotein, and some nucleoside reverse transcriptase inhibitors (NRTIs), notably stavudine, may be associated with the development of lipodystrophy.

Benefits and harms

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens versus standard protease inhibitor (PI)-based triple regimens:

See option on standard protease inhibitor-based triple regimens, p 16 .

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens versus boosted protease inhibitor (PI)-based regimens:

See option on boosted protease inhibitor-based triple regimens, p 9 .

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens versus nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens:

We found no systematic review comparing NNRTI-based triple regimens versus NRTI triple regimens. We found one RCT (1147 people who had not previously received antiretroviral treatment) comparing three treatments: an NNRTI -based triple regimen (lamivudine plus zidovudine plus efavirenz), an NRTI triple regimen (abacavir plus lamivudine plus zidovudine), and a quadruple regimen (abacavir plus lamivudine plus zidovudine plus efavirenz). [22] The RCT was stopped prematurely by the Data and Safety Monitoring Board when interim analysis found the triple NRTI regimen virologically inferior to the regimens containing efavirenz. At this point, the data in the two efavirenz-containing arms (2 or 3 NRTIs plus efavirenz) were pooled and compared with the triple NRTI data.

Progression to AIDS or mortality

No data from the following reference on this outcome. [22]

Markers of disease progression

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens compared with nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens NNRTI triple regimens may be more effective at reducing virological failure at 32 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Markers of disease progression					
[22] RCT **3-armed trial**	1147 people who had not previously received antiretroviral treatment Results for two arms pooled in analysis	**Virological failure , 32 weeks** 85/765 (11%) with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (includes lamivudine plus zidovudine plus efavirenz arm and abacavir plus lamivudine plus zidovudine plus efavirenz arm) 82/382 (21%) with triple nucleoside reverse transcriptase inhibitor (NRTI) regimen (abacavir plus lamivudine plus zidovudine arm)	P value not reported RCT was stopped prematurely by the Data and Safety Monitoring Board when interim analysis found the triple NRTI regimen virologically inferior to the regimens containing efavirenz		
[22] RCT **3-armed trial**	1147 people who had not previously received antiretroviral treatment Results for two arms pooled in analysis	**Time to virological failure** with NNRTI-based regimens (includes lamivudine plus zidovudine plus efavirenz arm and abacavir plus lamivudine plus zidovudine plus efavirenz arm) with triple NRTI regimen (abacavir plus lamivudine plus zidovudine arm) Absolute results reported graphically	P = 0.6 RCT was stopped prematurely by the Data and Safety Monitoring Board when interim analysis found the triple NRTI regimen virologically inferior to the regimens containing efavirenz	○○○	NNRTI-based regimens
[22] RCT **3-armed trial**	1147 people who had not previously received antiretroviral treatment Results for two arms pooled in analysis	**Changes in CD4 cell count** with NNRTI-based regimens (includes lamivudine plus zidovudine plus efavirenz arm and abacavir plus lamivudine plus zidovudine plus efavirenz arm) with triple NRTI regimen (abacavir plus lamivudine plus zidovudine arm)	P <0.001 RCT was stopped prematurely by the Data and Safety Monitoring Board when interim analysis found the triple NRTI regimen virologically inferior to the regimens containing efavirenz	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [22]

Further information on studies

Comment:

Lipodystrophy syndrome:
See option on standard protease inhibitor-based triple regimens, p 16 .

Hyperlactaemia and lactic acidosis:
See option on standard protease inhibitor-based triple regimens, p 16 .

Clinical guide:
Regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been recommended by some national panels for treatment in early disease. [20] [21] However, there is not a strong evidence-base for this stratagem. The choice of initial therapy is a consideration of the specific circumstances of the individual patient, and is a decision made jointly between patient and clinician.

OPTION NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI)-BASED TRIPLE REGIMENS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Triple antiretroviral treatments are now standard for people with HIV infection.
- Nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens offer similar viral suppression to standard protease inhibitor (PI)-based triple regimens.
- Some NRTIs (stavudine) may be associated with lipodystrophy.
- We found no clinically important results about NRTI triple regimens compared with boosted PI-based regimens.

Benefits and harms

Nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens versus standard protease inhibitor (PI)-based triple regimens:

See option on standard protease inhibitor-based triple regimens, p 16 .

Nucleoside reverse transcriptase inhibitor (NRTI) triple regimens versus boosted protease inhibitor (PI)-based regimens:

We found no systematic review or RCTs.

Nucleoside reverse transcriptase inhibitor (NRTI) triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens:

See option on NNRTI-based triple regimens, p 14 .

Further information on studies

Comment:

Lipodystrophy syndrome:
See option on standard protease inhibitor-based triple regimens, p 16 .

Hyperlactataemia and lactic acidosis:
See option on standard protease inhibitor-based triple regimens, p 16 .

OPTION STANDARD PROTEASE INHIBITOR-BASED TRIPLE REGIMENS

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- Triple antiretroviral treatments are now standard for people with HIV infection.
- Standard protease inhibitor-based triple regimens may be less effective than NNRTI-based triple regimens at reducing viral load.

Benefits and harms

Standard protease inhibitor (PI)-based triple regimens versus boosted PI-based regimens:

See boosted protease inhibitor-based regimens.

Standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens:

We found one systematic review (search date 1997–2005, 12 RCTs, 3337 people, range of duration of trials of 32 to 192 weeks) [19] and one additional RCT [23] comparing standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens. [19] Ten of the RCTs identified by the review were open label, and five were published only as abstracts.

Progression to AIDS or mortality

Standard protease inhibitor (PI)-based triple regimens compared with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens Standard PI-based triple regimens and NNRTI-based triple regimens seem equally effective at reducing death or disease progression (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Death or disease progression					
[19] Systematic review	2726 people 11 RCTs in meta-analysis	**Death or disease progression** 40/1380 (2.9%) with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimen 45/1346 (3.3%) with protease inhibitor (PI)-based triple regimen	OR for NNRTI *v* PI 0.87 95% CI 0.56 to 1.35 The review included ritonavir given in boosting doses as one PI, and did not carry out a subgroup analysis excluding boosted PI-based triple regimens for the outcome of death or disease progression	⟷	Not significant

Markers of disease progression

Standard protease inhibitor (PI)-based triple regimens compared with non-nucleoside reverse transcriptase (NNRTI)-based triple regimens Standard PI-based triple regimens may be less effective than NNRTI-based triple regimens at virological suppression (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Markers of disease progression					
[19] Systematic review	3337 people 12 RCTs in meta-analysis	**Virological suppression** 984/1680 (59%) with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimen 804/1657 (49%) with protease inhibitor (PI)-based triple regimen	OR for NNRTI *v* PI 1.60 95% CI 1.31 to 1.96 Subgroup analysis stratified by individual PI found similar results with the exception of atazanavir, for which there was no significant difference between groups. It also performed a subgroup analysis by NNRTI used and found similar results. See further information on studies The review found significant heterogeneity among studies for the analysis of virological suppression (P = 0.08). Factors associated with heterogeneity were the use of blinding, adequate randomisation, adequate allocation concealment, and proportion of people with AIDS	●○○	NNRTI-based triple regimen
[19] Systematic review	1425 people Subgroup analysis Subgroup analysis including only blinded RCTs 2 RCTs in analysis	**Virological suppression** with NNRTI-based triple regimen with PI-based triple regimen Absolute results not reported	OR 1.18 95% CI 0.95 to 1.46	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	915 people Subgroup analysis Subgroup analysis including only RCTs with adequate randomisation 3 RCTs in analysis	**Virological suppression** with NNRTI-based triple regimen with PI-based triple regimen Absolute results not reported	OR 1.18 95% CI 0.91 to 1.53	⟷	Not significant
[19] Systematic review	1862 people Subgroup analysis Subgroup analysis including only RCTs with adequate allocation concealment 5 RCTs in analysis	**Virological response** with NNRTI-based triple regimen with PI-based triple regimen Absolute results not reported	OR 1.25 95% CI 1.04 to 1.51	●○○	NNRTI-based triple regimen
[23] RCT	138 NNRTI -naive people who had achieved viral suppression (<50 copies/mL for 6 months) on a standard PI-based triple regimen	**Viral suppression (AR for loss of viral suppression) , 6 months** 6/34 (18%) with continuing the standard PI-based triple regimen 4/104 (4%) with changing to a NNRTI (nevirapine)-based triple regimen	P = 0.015	○○○	NNRTI-based triple regimen

Quality of life

Standard protease inhibitor (PI)-based triple regimens compared with non-nucleoside reverse transcriptase (NNRTI)-based triple regimens Standard PI-based triple regimens may be less effective at improving McGill Quality of Life Questionnaire scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[23] RCT	138 non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive people who had achieved viral suppression (<50 copies/mL for 6 months) on a standard protease inhibitor (PI)-based triple regimen	**Quality of life score (McGill Quality of Life Questionnaire, mean score range 0 [worst] to 10 [best])** 4.4 with PI-based triple regimen 9.1 with NNRTI-based triple regimen	P <0.01	○○○	NNRTI-based triple regimen

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] Systematic review	2668 people 10 RCTs in meta-analysis	**Withdrawals attributable to adverse effects** 124/1351 (9%) with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimen	OR for NNRTI *v* PI 0.68 95% CI 0.43 to 1.08 The review found significant heterogeneity among studies included in the meta-analysis	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		145/1317 (11%) with protease inhibitor (PI)-based triple regimen	(P = 0.005). Use of blinding and adequate allocation concealment were associated with heterogeneity The review gave no information on individual adverse effects associated with either drug regimen		
[19] Systematic review	1425 people Subgroup analysis Subgroup analysis of blinded RCTs 2 RCTs in meta-analysis	**Withdrawals attributable to adverse effects** with NNRTI-based triple regimen with PI-based triple regimen Absolute results not reported	OR 1.40 95% CI 0.95 to 2.06	⟷	Not significant
[19] Systematic review	1862 people Subgroup analysis Subgroup analysis of RCTs with adequate allocation concealment 5 RCTs in meta-analysis	**Withdrawals attributable to adverse effects** with NNRTI-based triple regimen with PI-based triple regimen Absolute results not reported	OR 1.20 95% CI 0.87 to 1.64	⟷	Not significant
[24]		**Lipodystrophy syndrome** with NNRTI-based triple regimen with PI-based triple regimen There is increasing concern about the association of antiretroviral treatment and lipodystrophy. See further information on studies			
[25] [26]		**Hyperlactataemia and lactic acidosis** with NNRTI-based triple regimen with PI-based triple regimen Lactic acidosis is increasingly a concern as a potential adverse effects of antiretroviral treatment. See further information on studies			

Standard protease inhibitor (PI)-based triple regimens versus nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens:

We found one multicentre RCT, which compared a triple NRTI regimen (abacavir plus lamivudine plus zidovudine) versus a standard PI-based triple regimen (lamivudine plus zidovudine plus indinavir [PI]). [27]

Progression to AIDS or mortality

No data from the following reference on this outcome. [27]

Markers of disease progression

Standard protease inhibitor (PI)-based triple regimens compared with nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens Standard PI-based triple regimens and NRTI-based triple regimens seem equally effective at improving CD4 cell count and virological suppression at 48 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Markers of disease progression					
[27] RCT	562 antiretroviral-naive people	**Viral suppression (AR for <400 copies/mL HIV RNA) , 48 weeks** 136/265 (51.3%) with protease inhibitor (PI)-based triple regimen 133/262 (50.8%) with nucleoside reverse transcriptase inhibitor (NRTI) triple regimen	Mean difference –0.6% 95% CI –9.0% to +8.0%	⟷	Not significant
[27] RCT	562 antiretroviral-naive people	**Median improvement in CD4 cell count , 48 weeks** with PI-based triple regimen with NRTI triple regimen Absolute results reported graphically	Mean difference –3 cells/mm^3 95% CI –24 cells/mm^3 to +19 cells/mm^3	⟷	Not significant
[27] RCT	205 antiretroviral-naive people Subgroup analysis Prespecified subgroup analysis in people with a high viral load at baseline (>100,000 copies/mL HIV RNA)	**Viral suppression (<400 copies/mL HIV RNA) , 48 weeks** with PI-based triple regimen with NRTI triple regimen Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant
[27] RCT	205 antiretroviral-naive people Subgroup analysis Prespecified subgroup analysis in people with a high viral load at baseline (>100,000 copies/mL HIV RNA)	**Viral suppression (<50 copies/mL HIV RNA) , 48 weeks** 45/100 (45%) with PI-based triple regimen 30/96 (31%) with NRTI triple regimen	Mean difference –14% 95% CI –27% to 0%	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] RCT	562 antiretroviral-naive people	**Deaths attributable to treatment** 1 with protease inhibitor (PI)-based triple regimen 3 with nucleoside reverse transcriptase inhibitor (NRTI) triple regimen In the triple NRTI regimen group, one death was due to hypersen-	Statistical comparison between groups not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		sitivity, and two due to MI. The death in the standard PI-based triple regimen group was thought to be associated with recreational drug misuse			
[27] RCT	562 antiretroviral-naive people	**Adverse effects leading to discontinuation of treatment** 58/264 (22%) with PI-based triple regimen 45/262 (17%) with NRTI triple regimen	Reported as not significant P value not reported	⟷	Not significant
[27] RCT	562 antiretroviral-naive people	**Nausea, grade 2–4** 16% with PI-based triple regimen 14% with NRTI triple regimen	Statistical comparison between groups not reported		
[27] RCT	562 antiretroviral-naive people	**Nausea and vomiting, grade 2–4** 8% with PI-based triple regimen 8% with NRTI triple regimen	Statistical comparison between groups not reported		
[27] RCT	562 antiretroviral-naive people	**Fatigue and malaise, grade 2–4** 10% with PI-based triple regimen 10% with NRTI triple regimen	Statistical comparison between groups not reported		
[27] RCT	562 antiretroviral-naive people	**Headache, grade 2–4** 5% with PI-based triple regimen 10% with NRTI triple regimen	Statistical comparison between groups not reported		
[27] RCT	562 antiretroviral-naive people	**Renal symptoms, grade 2–4** 5% with PI-based triple regimen 1% with NRTI triple regimen	Statistical comparison between groups not reported		
[24]		**Lipodystrophy syndrome** with PI-based triple regimen with NRTI triple regimen There is increasing concern about the association between antiretroviral treatment and lipodystrophy syndrome. See further information on studies			
[25] [26]		**Hyperlactataemia and lactic acidosis** with PI-based triple regimen with NRTI triple regimen Lactic acidosis is increasingly a concern as a potential adverse effect of antiretroviral treatment. See further information on studies			

Further information on studies

[19] **Subgroup analysis: Standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens** The review also did a subgroup analysis by individual

PI for virological suppression. [19] Subgroup analyses stratified by individual PI added found similar results to the overall analysis, with the exception of atazanavir, for which there was no significant difference between treatment groups (nelfinavir [5 RCTs, 1581 people]: OR 1.53, 95% 1.09 to 2.15; indinavir [3 RCTs, 541 people]: OR 1.82, 95% CI 1.20 to 2.74; atazanavir [1 RCT, 805 people]: OR 1.25, 95% CI 0.93 to 1.66; absolute numbers not reported). The review also carried out subgroup analyses of virological suppression based on the NNRTI used (either efavirenz or nevirapine). Subgroup analyses found the standard PI-based triple regimen significantly less effective at virological suppression than both the efavirenz- and nevirapine-based triple regimens (OR for NNRTI-based *v* PI-based triple regimens: efavirenz [9 RCTs, 2956 people]: OR 1.64, 95% CI 1.28 to 2.10; nevirapine [3 RCTs, 381 people]: OR 1.57, 95% CI 1.05 to 2.36; absolute numbers not reported).

[24] [28] [29] [30] [31] [32] [33] [34] [35]

Lipodystrophy syndrome There is increasing concern about the association between antiretroviral treatment and lipodystrophy syndrome. [24] This syndrome consists of elevated serum lipid levels, redistribution of fat storage in the body leading to changes in body shape (morphological lipodystrophy), and insulin resistance. One systematic review (search date 2002, 14 RCTs, 57 observational studies, narrative synthesis only) concluded that there was evidence that use of PI-based regimens was associated with increased serum levels of total cholesterol, triglycerides, and low-density lipoprotein, and with morphological changes in vasculature known to be associated with increased cardiovascular risk (carotid intima thickening or presence of atherosclerotic lesions). [29] Preliminary evidence from long-term observational studies suggested that PI use may increase the risk of MI. [29] Morphological lipodystrophy is often a cause of psychological distress, loss of quality of life, and treatment non-adherence in people on highly active antiretroviral therapy. [24] [28] There is considerable variability in the definition of syndromes involving body fat distribution anomalies. [30] Therefore, estimates of the prevalence of morphological lipodystrophy differ. Prospective observational studies suggest that some patterns of adipose tissue maldistribution may be associated with high adherence to treatment, increasing age, and female sex. [28] [31] [32] Although morphological lipodystrophy was initially thought to be associated with PI use, some nucleoside reverse transcriptase inhibitors (NRTIs), notably stavudine, have also been suggested to have a role in their development. [31] [32] [25] [33] Observational studies have estimated that, in people receiving PI-based antiretroviral treatment, the prevalence of diabetes is about 6%–7%, whereas 16%–18% have impaired glucose tolerance. [34] [35] Further studies are needed on the issue of glucose intolerance.

[25] [26] [36] [37] [38]

Hyperlactataemia and lactic acidosis Lactic acidosis is increasingly a concern as a potential adverse effect of antiretroviral treatment. [25] [26] One systematic review (search date 2001) identified 217 published cases of lactic acidosis in people with HIV. [26] It found that all the people for whom data were available (90 cases) were taking NRTIs at the time of the episode. The review estimated that women may be at higher risk than men for lactic acidosis (RR 2.5, CI not reported). [26] One small case control study compared 11 people with hyperlactataemia and HIV (cases) with 118 people with HIV but no hyperlactataemia (controls). [36] It found no significant difference in the use of NRTIs or PIs between cases and controls (AR for any NRTI regimen: 100% in cases *v* 81% in controls; P = 0.21; AR for any PI treatment: 55% in cases *v* 42% in controls; P = 0.53). However, people with hyperlactataemia were significantly more likely than people without hyperlactataemia to be receiving didanosine or stavudine (AR for didanosine treatment: 82% in cases *v* 19% in controls; P <0.0001; AR for stavudine treatment: 82% in cases *v* 48% in controls; P = 0.03). One person with hyperlactataemia developed lactic acidosis and died. Another case control study compared 267 people with HIV and at least one episode of hyperlactataemia over the previous 6 months (cases) with 476 people with HIV and no episodes of hyperlactataemia over the previous 6 months (controls). [37] It found no significant difference between cases and controls in current or previous antiretroviral regimen use (no further data reported). However, it found that, compared with controls, cases had significantly longer duration of antiretroviral use (27.5 months with cases *v* 25.0 months with controls; P <0.004) and highly active antiretroviral therapy use (20.1 months with cases *v* 18.3 months with controls; P <0.003). Four of 52 (8%) people with sustained hyperlactataemia developed lactic acidosis. Multivariate analysis in one cohort study (1204 people taking antiretroviral treatment for at least 4 months) found that regimens containing didanosine significantly increased the risk of hyperlactataemia compared with regimens without didanosine (HR 2.13, CI displayed graphically). [38] Regimens containing abacavir significantly reduced the risk of hyperlactataemia compared with regimens without abacavir (HR 0.40, CI displayed graphically). However, the authors concluded that screening of lactate levels in people on antiretroviral treatment without symptoms of lactic acidosis is of limited use. [38] Mortality among people with lactic acidosis is high.

Comment: None.

OPTION EARLY VERSUS DELAYED ANTIRETROVIRAL TREATMENT

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- We don't know whether early initiation of antiretroviral treatment using triple regimens improves long-term survival.
- The decision about when to start treatment currently depends on severity of symptoms and on CD4 lymphocyte count, so that likely benefits can be balanced against risks of adverse effects of treatment.

Benefits and harms

Early versus delayed triple-drug antiretroviral treatment:

We found one RCT comparing the long-term advantages of commencing highly active antiretroviral therapy (HAART) (stavudine 40 mg plus lamivudine 150 mg plus nevirapine 200 mg) at different CD4 lymphocyte thresholds. [39] CD4 count was monitored every 8 weeks.

Progression to AIDS or mortality

No data from the following reference on this outcome. [39]

Markers of disease progression

Early compared with delayed triple drug antiretroviral treatment Starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple therapy at a CD4 count of fewer than 200 cells/mm^3 may be more effective at improving CD4 cell counts but not mortality (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mean CD4 cell count response					
[39] RCT **3-armed trial**	100 antiretroviral-naive people with HIV with CD4 count of 100–500 cells/mm^3 (<200 cells/mm^3 [48 people]; 200–350 cells/mm^3 [36 people]; >350 cells/mm^3 [16 people])	**Mean CD4 count response (mean increase in CD4 count [cells/mm^3]) , 48 weeks** 163 with pretherapeutic CD4 count of <200 118 with pretherapeutic CD4 count of 200–350 50 with pretherapeutic CD4 count of >350	P <0.05 Method of randomisation, blinding, and loss to follow-up unclear	○○○	commencing highly active antiretroviral therapy with pretherapeutic CD4 count of <200 cells/mm^3

Quality of life

No data from the following reference on this outcome. [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39]	100 antiretroviral-naive people with HIV with CD4 count of 100–500 cells/mm^3 (<200 cells/mm^3 [48 people]; 200–350 cells/mm^3 [36 people]; >350 cells/mm^3 [16 people])	**Development of Stevens-Johnson syndrome** with pretherapeutic CD4 count of <200 with pretherapeutic CD4 count of 200–350 with pretherapeutic CD4 count of >350 The RCT reported that 15% (absolute numbers not reported) of people on highly active antiretroviral therapy developed Stevens–Johnson syndrome	Significance between groups not assessed		

Early versus delayed zidovudine monotherapy:

We found one systematic review (search date not reported, 9 RCTs) comparing zidovudine given immediately versus zidovudine deferred until the early signs of AIDS. [40]

Progression to AIDS or mortality

Early compared with delayed zidovudine monotherapy We don't know whether immediate treatment with zidovudine monotherapy is more effective than deferred treatment with zodovudine monotherapy at improving the composite outcome of progression to AIDS or death or overall survival in people with asymptomatic or mildly symptomatic HIV, mainly with CD4 cell counts more than 200/mm^3 (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Progression to AIDS or mortality					
[40] Systematic review	7722 people with asymptomatic or mildly symptomatic HIV, mainly with CD4 cell counts >200/mm^3	**Progression to AIDS or death , 1 year** 78/4431 (2%) with immediate zidovudine 131/3291 (4%) with deferred zidovudine	OR 0.52 95% CI 0.39 to 0.68	●○○	immediate zidovudine monotherapy
[40] Systematic review	7722 people with asymptomatic or mildly symptomatic HIV, mainly with CD4 cell counts >200/mm^3	**Progression to AIDS or death at end of follow-up , median follow-up of 50 months** 1026/4431 (23%) with immediate zidovudine 882/3291 (27%) with deferred zidovudine	OR 0.96 95% CI 0.87 to 1.05	⟷	Not significant
[40] Systematic review	7722 people with asymptomatic or mildly symptomatic HIV, mainly with CD4 cell counts >200/mm^3	**Overall survival , 1 year** 24/4431 (0.5%) with immediate zidovudine 18/3291 (0.6%) with deferred zidovudine	OR 1.22 95% CI 0.67 to 2.25	⟷	Not significant
[40] Systematic review	7722 people with asymptomatic or mildly symptomatic HIV, mainly with CD4 cell counts >200/mm^3	**Overall survival at end of follow-up , median follow-up of 50 months** 734/4431 (17%) with immediate zidovudine 617/3291 (19%) with deferred zidovudine	OR 1.04 95% CI 0.93 to 1.16	⟷	Not significant

No data from the following reference on this outcome. [40]

Markers of disease progression

No data from the following reference on this outcome. [40]

Quality of life

No data from the following reference on this outcome. [40]

Adverse effects

No data from the following reference on this outcome. [40]

Further information on studies

[39] The RCT reported mortality to be 3%, with deaths being clustered among people who initiated highly active antiretroviral therapy (HAART) with a pretherapeutic CD4 count of fewer than 200 cells/mm^3.

[41] **Adverse effects: Early versus delayed zidovudine monotherapy** Another systematic review (search date 1994, 9 RCTs), also comparing zidovudine given immediately versus zidovudine deferred until the early signs of AIDS, presented pooled toxicity data in terms of events/100 person years. [41] In asymptomatic people, early treatment conferred a small but significant increase in the risk of severe anaemia (500–1000 mg/day zidovudine; 5 RCTs; RR of haemoglobin <8.0 g/dL: early *v* deferred treatment 2.1, 95% CI 1.1 to 4.1; ARI 0.4 events per 100 person-years; no further data reported). It also found that early treatment significantly increased the risk of severe anaemia in symptomatic people; this excess probably reflected the high doses of zidovudine used (1200–1500 mg/day; 3 RCTs; RR of severe anaemia: early *v* deferred treatment 3.6, 95% CI 1.3 to 10.0; no further data reported). There was also a small increase in risk of neutropenia in asymptomatic people with early treatment (ARI 1.1 events/100 person years; P = 0.07; no further data reported). The authors advised that the toxicity results should be interpreted with caution, because the results varied considerably between trials (no heterogeneity statistic reported).

Comment: The RCTs included in the systematic review were all started when zidovudine was the only antiretroviral drug available. With triple-drug regimens, treatment is known to be beneficial up to and over a 2-year period from treatment initiation. This is important to consider when making the decision as to when to commence treatment. Decisions on when to initiate multidrug treatment are currently based on our understanding of how HIV induces immune damage, the capacity for immune regeneration while on treatment, the toxicity and inconvenience of treatment, and the risk of resistance, and not on the results of RCTs. After initial moderate differences, guidelines from national bodies in the USA and the UK on when to start treatment seem gradually to be approaching a consensus. Yet both recognise that the quality of evidence is poor. [21] [42] People with symptomatic, late-stage, chronic disease should be treated. Treatment may be offered to those with severe symptoms in primary infection (the so-called seroconversion illness) but there is no evidence that, at that stage, treatment either prevents onward virus transmission or delays ultimate disease progression. In asymptomatic late disease, the arbiter is the CD4 lymphocyte count. Treatment is usually offered to those with sustained counts of fewer than 200 cells/mm^3, but not to those with counts of more than 350 cells/mm^3. Between these levels, treatment might be offered, weighing up risks with benefits, depending on viral load, the rate of fall of the CD4 cell count, and the readiness of the person to engage meaningfully with treatment. There has been a call for the initiation of treatment at a CD4 count of 350 cells/mm^3. [43] The argument has been made that the reasons for delaying treatment (inconvenience to the patient, toxicity, relative risk of developing AIDS at higher counts, and advances in treatment) have been undermined in the light of recent evidence from the SMART trial [44] and findings that have led to a greater understanding of toxicity management and of adherence support. The SMART study was terminated prematurely when patients in the episodic-treatment arm were shown to be at greater risk of AIDS and death than patients in the continuous arm. People with hepatitis C co-infection should be treated earlier rather than later.

OPTION COMBINATION TREATMENTS CONTAINING FUSION INHIBITORS (ENFUVIRTIDE) New

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- We don't know whether combination treatments containing fusion inhibitors (enfuvirtide) improve long-term survival.

Benefits and harms

Combination treatments containing fusion inhibitors (enfuvirtide):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Fusion inhibitors are newer drugs. Evidence of their effectiveness is growing, but their use as therapies is generally restricted to people for whom therapeutic options are otherwise limited because of virological failure, high levels of ARV resistance, or intolerance to standard agents.

OPTION COMBINATION TREATMENTS CONTAINING CHEMOKINE (C-C MOTIF) RECEPTOR 5 INHIBITORS New

- For GRADE evaluation of interventions for HIV infection, see table, p 29 .
- We don't know whether combination treatments containing chemokine (C-C motif) receptor 5 inhibitors improve long-term survival.

Benefits and harms

Combination treatments containing chemokine (C-C motif) receptor 5 inhibitors:
We found no systematic review or RCTs.

Further information on studies

Comment: Co-receptor antagonists are newer drugs. Evidence of their effectiveness is growing, but their use as therapies is generally restricted to people for whom therapeutic options are otherwise limited because of virological failure, high levels of ARV resistance, or intolerance to standard agents.

GLOSSARY

Highly active antiretroviral therapy (HAART) Therapy consisting of two nucleoside reverse transcriptase inhibitors plus one or two protease inhibitor(s), or plus one non-nucleoside reverse transcriptase inhibitor.

Protease inhibitor A class of antiretroviral drugs inhibiting the viral enzyme protease (which is involved with the making of new viral protein within the host cell).

Antiretroviral Drug interfering with HIV replication: may act at one of several sites in the host cell.

Boosted protease inhibitor-based regimen Antiretroviral regimen consisting of two nucleoside reverse transcriptase inhibitors plus a protease inhibitor, plus the protease inhibitor ritonavir.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimen Antiretroviral regimen consisting of two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor.

Nucleoside reverse transcriptase inhibitor (NRTI) A class of nucleoside-based antiretroviral drugs inhibiting the viral enzyme reverse transcriptase (which converts viral RNA to DNA within the host cell).

Protease inhibitor-based triple regimen Antiretroviral regimen consisting of two nucleoside reverse transcriptase inhibitors and a protease inhibitor.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Combination treatments containing fusion inhibitors (enfuvirtide) New option for which we identified no RCTs. Categorised as Unknown effectiveness.

Combination treatments containing chemokine (C-C motif) receptor 5 inhibitors New option for which we identified no RCTs. Categorised as Unknown effectiveness.

Boosted protease inhibitor-based triple regimens One systematic review added: [19] benefits and harms data enhanced; categorisation unchanged (Beneficial). The review found that ritonavir-boosted protease inhibitor-based triple regimens were significantly less effective than NNRTI-based triple regimens at virological suppression.

Early versus delayed antiretroviral treatment using triple antiretroviral regimens One RCT on the effects of early versus late triple therapy regimens added: [39] benefits and harms data enhanced; the RCT found a greater improvement in CD4 count when starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple therapy at a CD4 count of <200 cells/mm^3 compared with CD4 counts of 200–350 cells/mm^3 and of >350 cells/mm^3. However, all deaths before the end of treatment occurred in the group with pretherapeutic CD4 count of <200 cells/mm^3.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens One systematic review added: [19] benefits and harms data enhanced. The review found that NNRTI-based triple regimens were significantly more effective at virological suppression than ritonavir-boosted protease inhibitor (PI)-based triple regimens. The review found a significantly higher rate of virological suppression with NNRTI-based triple regimens compared with PI-based triple regimens. The review found no significant difference in death or disease progression between NNRTI-based triple regimens and PI-based triple regimens. However, PI regimes in this analysis included regimens in which ritonavir had been given in boosting doses with a PI.

Postexposure prophylaxis in healthcare workers One systematic review added: [11] benefits and harms data enhanced; categorisation unchanged (Likely to be beneficial by consensus). The review identified no RCTs on the effects of postexposure prophylaxis in healthcare workers.

Standard protease inhibitor (PI)-based triple regimens One systematic review comparing NNRTI-based triple regimens versus standard PI-based triple regimens added: [19] benefits and harms data enhanced. The review found a significantly lower rate of virological suppression with standard PI-based triple regimen compared with NNRTI-based triple regimen. The review found no significant difference in death or disease progression between standard PI-based triple regimens and NNRTI-based triple regimens. However, PI regimes in this analysis included regimens in which ritonavir had been given in boosting doses with a PI.

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Disclaimer

GRADE **Evaluation of interventions for HIV infection.**

Important outcomes	Incidence of HIV infection, Markers of disease progression, Progression to AIDS or mortality, Quality of life								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to prevent transmission of HIV?									
3 (23,432) [7] [8] [9] [10]	Incidence of HIV infection	Early diagnosis and treatment of STDs versus control	4	–1	–1	–2	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness points deducted for wide range of comparators and differences in status of epidemics
1 (712) [12]	Incidence of HIV infection	Zidovudine alone versus control	2	–1	0	–1	+2	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of comparators. Effect-size points added for odds ratio (OR) less than 0.2
2 (13,192) [7] [14] [15]	Incidence of HIV infection	Presumptive mass treatment of STDs versus control	4	0	0	–2	0	Low	Directness points deducted for inclusion of people with HIV in one RCT and for inclusion of co-interventions in one group
What are the effects of different antiretroviral drug treatment regimens in HIV infection?									
1 (318) [18]	Progression to AIDS or mortality	Boosted protease inhibitor (PI)-based triple regimens versus standard PI-based triple regimens	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about treatment regimen
3 (1018) [16] [17] [18]	Markers of disease progression	Boosted protease inhibitor (PI)-based triple regimens versus standard PI-based triple regimens	4	0	–1	–1	0	Low	Consistency point deducted for no consistent evidence of benefit. Directness point deducted for uncertainties about treatment regimens in one RCT
3 (410) [19]	Markers of disease progression	Boosted protease inhibitor (PI)-based regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz or nevirapine)-based triple regimens	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for open label RCTs
1 (1147) [22]	Markers of disease progression	Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens versus nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for early termination
11 (2726) [19]	Progression to AIDS or mortality	Standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens	4	–1	0	–1	0	Low	Quality point deducted for open label RCTs. Directness point deducted for mixed intervention
12 (3337) [19]	Markers of disease progression	Standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens	4	–2	0	–1	0	Very low	Quality points deducted for heterogeneity between RCTs and inclusion of open label RCTs. Directness point deducted for mixed intervention

Important outcomes	Incidence of HIV infection, Markers of disease progression, Progression to AIDS or mortality, Quality of life								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (138) [23]	Quality of life	Standard protease inhibitor (PI)-based triple regimens versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based triple regimens	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (562) [27]	Markers of disease progression	Standard protease inhibitor (PI)-based triple regimens versus nucleoside reverse transcriptase inhibitor (NRTI)-based triple regimens	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (100) [39]	Markers of disease progression	Early versus delayed triple-drug antiretroviral treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data and methodological uncertainties (blinding, method of randomisation, and loss to follow-up)
1 (7722)	Progression to AIDS or mortality	Early versus delayed zidovudine monotherapy	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness points deducted for restricted population and for uncertain clinical relevance (trial started when zidovudine was the only antiretroviral drug available)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.